8923 (hereinafter, the "Nickerson reference"), and 4) U.S. Patent No. 6,127,191 (hereinafter, the "Graybill reference").

Claims 83-87 also are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the combination of the following references: 1) the Agrafiotis reference, 2) the Hyndman reference, 3) the Nickerson reference, 4) U.S. Patent No. 5,352,775 (hereinafter, the "Albertsen reference"), 5) U.S. Patent No. 5,407,796 (hereinafter, the "Cutting reference"), and 6) the Graybill reference.

The Office Action mistakenly asserts that it would have been *prima facie* obvious for one skilled in the art to generate a virtual library of compounds in the system of Agrafiotis, Hyndman, and Nickerson (also taking into consideration the Albertsen and/or Cutting references) where the motivation would have been to select compounds for synthesis which best reflect the desired properties (Graybill). Applicants traverse the rejection and respectfully request reconsideration because there is no motivation to combine the cited references and, even if combined, the claimed invention would not be produced.

Applicants' claimed invention differs from the Agrafiotis reference because, *inter alia*, the Agrafiotis reference describes generating a directed diversity chemical library where the number of compounds must increase with each iteration since additional compounds are synthesized for a new directed diversity chemical library. Further, at no point does the Agrafiotis reference, alone or in combination with the Hyndman and/or Nickerson references, describe creating a virtual library of oligonucleotides, and then reducing the number of members in the virtual library using the criteria recited in the instant claims, followed by synthesis of only those compounds that remain following the reduction step. The addition of the Albertsen and/or Cutting references also fails to teach reducing the number of members in the virtual library using the criteria recited in the instant claims. Rather, the Agrafiotis reference teaches synthesizing and testing all members of the library as actual compounds once the chemical building blocks are selected. In the Agrafiotis process, initialization occurs by selecting a particular set of chemical building blocks "aimed at maximizing the information content of the resulting chemical library" (see, col. 16, lines 64-66). Once selected, the selected building blocks are combined to physically synthesize all combinations of the compounds (see, col. 5, lines 31-45; col. 22, lines 13-40).

Thus, the Agrafiotis reference teaches physically synthesizing all compounds during initialization so that the number of oligonucleotide sequences in a virtual library is not reduced prior to synthesis. The synthesized compounds are analyzed to obtain structure-activity data (SAR) (see, Fig. 2; col. 5, lines 56-64), and the collected SAR and historical SAR are subsequently used to synthesize additional compounds for a new directed diversity chemical library (see, Fig. 2; col. 6, lines 49-53; col. 22, lines 41-67; col. 23, lines 1-30).

In contrast, Applicant's claimed invention relies on a system that first prepares the virtual library of oligonucleotide sequences and then reduces the number of oligonucleotide sequences in the virtual library of oligonucleotide sequences, and instructs an automated synthesizer that synthesizes only that set of real oligonucleotides that corresponds to the virtual set of oligonucleotide sequences consisting of said reduced number of oligonucleotide sequences. Contrary to the Agrafiotis reference, Applicant's claimed invention prepares a virtual library of oligonucleotide sequences consisting of, for example X sequences, reduces the number of oligonucleotide sequences in the virtual library, and instructs an automated synthesizer that synthesizes a set of real oligonucleotides consisting of, for example Y sequences, so that, Y is less than X as a consequence of the reduction step.

The Hyndman reference does not cure the above-noted deficiencies in the Agrafiotis reference because the Hyndman reference, alone or in combination with the Agrafiotis reference, and the Nickerson reference, fails to teach or suggest all claim elements. The Hyndman reference reports a computer program (HYB*simulator*) that uses input criteria such as melt temperature, free energy and length to design a probe set against a target sequence, but then identifies preferred probes by eliminating sequences with insufficient target specificity (see, pages 1092, 1094, and Figure 4), or retaining probes expected to perform well in PCR amplifications. The Hyndman process does not teach or suggest reducing the number of oligonucleotide sequences in a virtual library using a process of selection based on targeting a functional region of the selected nucleic acid as recited in claim 83, nor reduction by one or more of i) a process of selection based on target accessibility to the selected nucleic acid, ii) a process of selection based on uniform distribution of oligonucleotide compounds across the selected nucleic acid, or iii) a process of selection based on targeting a functional region of the selected nucleic acid as recited

in claims 85-87. Thus, the Hyndman reference, alone or in combination with the Agrafiotis reference, does not teach or suggest all the elements of the claimed invention.

Further, the Nickerson reference merely reports testing of oligonucleotides using automated apparatus.

Thus, the combination of the Agrafiotis, Hyndman, and Nickerson references (and additionally the Albertsen and Cutting references) fails to produce Applicants' claimed invention.

The Office Action mistakenly takes the position that that the addition of the Graybill reference cures the deficiencies of the combination of the Agrafiotis, Hyndman, and Nickerson references (and the additional Albertsen and Cutting references). In particular, the Office Action asserts that the "DirectedDiversity®" program of the Graybill results in selection of compounds with desired properties wherein a virtual library of compounds is generated and then evaluated for specific physical and biological properties (referring to col. 14, lines 40-61). The Office Action, however, has taken this portion of the Graybill reference out of context. Indeed, the "DirectedDiversity®" program referred to in the portion of the Graybill reference referred to in the Office Action does not appear to carry out the process recited in claim 83, for example. Claim 83 recites that the "computer system first prepares said virtual library of oligonucleotide sequences and then reduces the number of oligonucleotide sequences in said virtual library of oligonucleotide sequences by a process of selection based on targeting a functional region of said selected nucleic acid." Rather, the "DirectedDiversity®" program of the Graybill reference is "an iterative drug refinement process that explores chemical space through successive rounds of sublibrary selection" (see, col. 14, lines 40-42). Further, the Graybill reference teaches that "if a first iteration of screening results in an active compound that contains a phenyl ring, then in subsequent iterations of the screen this aromatic residue can be varied using substituted phenyl groups in a stepwise manner" (see, col. 14, lines 33-37). The Graybill reference further teaches that a "preferred iterative method is DirectedDiversity®." Thus, there is no teaching whatsoever in the Graybill reference of any process that "reduces the number of oligonucleotide sequences in said virtual library of oligonucleotide sequences by a process of selection **based on targeting a functional region of said selected nucleic acid**" as recited in claim 83. Indeed, the

DirectedDiversity® program in the Graybill reference is used to prepare aminobenzenedicarboxylic acid-based combinatorial libraries wherein the iterations are carried out to refine particular chemical groups, such as phenyl groups, within the aminobenzenedicarboxylic acid compounds, **not** to reduce the number of oligonucleotide sequences in a virtual library of oligonucleotide sequences by a process of selection based on **targeting a functional region** of the selected nucleic acid. Thus, the addition of the Graybill reference to the combination of the Agrafiotis, Hyndman, and Nickerson references (and additionally the Albertsen and Cutting references) fails to produce Applicants' claimed invention.

Furthermore, Applicants respectfully submit that the proposed modification (i.e., reducing the number of oligonucleotide sequences in a virtual library of oligonucleotide sequences by a process of selection based on targeting a functional region of a selected nucleic acid) to the Agrafiotis reference is improper because it renders the Agrafiotis reference unsatisfactory for its intended purpose. Indeed, Agrafiotis' invention relies on synthesizing and collecting data using a set of compounds, followed by iteration and synthesis of additional compounds based on structure activity relationship data obtained from the initial set. As the Agrafiotis reference teaches, an initial set of building blocks is selected for making a directed diversity library. Those building blocks are selected to provide maximum information content:

> The initial choice is aimed at maximizing the information content of the resulting chemical library within the domain of interest, as measured by the presence of chemical functionalities, hydrogen bonding characteristics, electronic properties, topological and topographical parameters.

(the Agrafiotis reference at col. 16, line 64 to col. 17, line 2). Because the proposed modification to reduce *in silico* the members of the directed diversity library according to the criteria identified in the instantly claimed invention interferes with Agrafiotis' requirement to derive structure-activity models having enhanced predictive and discriminating capabilities it renders Agrafiotis unsatisfactory for its intended purpose, thus seriously undermining the Examiner's alleged reasons for motivation. The motivation therefore is improper. See, MPEP §2143.01.

Thus, the combination of the Agrafiotis, Hyndman, Nickerson, and/or the Albertsen and Cutting references with the addition of the Graybill reference does not disclose reducing the number of members of a virtual library of oligonucleotides based on i) a process of selection based on target accessibility to said selected nucleic acid, ii) a process of selection based on uniform distribution of oligonucleotide compounds across said selected nucleic acid, or iii) a process of selection based on targeting a functional region of said selected nucleic acid. Thus, the claimed invention is not obvious in view of the combination of cited references. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

II. Obviousness-Type Double Patenting

Claims 83 and 85-87 are provisionally rejected under the doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 55, 56, 58-72, 74-87, and 99-102 of co-pending application Serial No. 09/295,463. Applicants agree to execute a terminal disclaimer upon indication of allowable subject matter in the present application.

III. The Claimed Invention Is Supported by Ample Written Description

Claims 83-87 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing new matter. The Office Action asserts that "A system for preparing a set of oligonucleotides wherein a computer system FIRST prepares a virtual library of oligonucleotides sequences, then reduces the number of sequences, is new matter." The Office Action also asserts that Applicants failed to provide any support for the previously amended claims. Applicants traverse the rejection and respectfully request reconsideration because the specification provides ample written description supporting the claimed inventions.

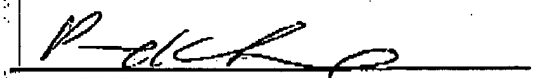
Applicants provided ample basis in the response filed February 11, 2005 for the amended claims -- support for the amendments can be found throughout the specification as filed, and at, for example, page 19, lines 10-25; page 22, line 33 to page 23, line 10; page 24, line 34 to page 26, line 22; page 65, line 25 to page 66, line 22; page 89, line 2 to page 94, line 4; page 103, line 16 to page 105, line 18; and Figures 1, 4, 5, 20 and 22.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, as allegedly providing new matter be withdrawn.

IV. Conclusion

In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at (215) 665-6914 if there are any questions regarding Applicants' claimed invention.

Respectfully submitted,



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